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S/N 09/125,953

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	FODSTAD et al.	Examiner:	Sisson, B.
Serial No.:	09/125,953	Group Art Unit:	1655
Filed:	December 10, 1998	Docket No.:	7885.56USWO
Title:	IMMUNO-MAGNETIC CELL SEPARATION USED IN IDENTIFICATION OF GENES ASSOCIATED		

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By:
Name: Chris Stordahl

AMENDMENT AND RESPONSE

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated May 4, 2001, with the time for response extended with a three month extension of time to November 4, 2001, please amend the afore-mentioned patent application as indicated herein.

In the Claims

Please amend claims 6,7, 8, 9, and 12 to read as follows. In view of rule changes to 37 C.F.R. §1.121, a clean version of amended claims 6,7, 8, 9, and 12 is presented as below. Also enclosed herewith is an attachment of a marked-up copy with revisions to show changes to claims 6,7, 8, 9, and 12.

6. (Amended) Method according to claim 5, further comprising the step of cloning the extracted nucleic acids.

E1 - sub F2

7. (Amended) Method according to claim 12, wherein the identification of differential gene expression is determined by differential display or subtractive hybridization.

8. (Amended) Method according to claim 7, wherein amplified cDNAs are obtained from malignant cells selected from the first and second tissues and are compared on sequencing gels, and wherein site-specific or site-preferenced patterns revealing differential expression are sequenced and identified.

E1 cont 3 of F3

9. (Amended) Method according to claim 8, wherein the expression pattern of identified gene sequences are studied on material obtained from two or more tumor sites.

12. (Amended) Method for identifying genes differentially expressed between cells isolated from different tissues, the method comprising:

(A) detecting target cells from a first and a second tissue;

(B) obtaining nearly 100% specific target cells by repeatedly immunomagnetically isolating, *in vitro*, said first and second tissue target cells;

E2

(C) determining levels of mRNA expression within said first and second tissue target cells;

(D) comparing the levels of mRNA expression in said first and second tissue target cells; and

(E) based upon the comparison in step D, identifying the genes differentially expressed between said first and second tissue target cells, wherein at least one of said first and second tissue target cells are tumor cells, in order to recognize previously unknown genes possibly involved in determining metastatic characteristics of cancer cells.

Remarks

Reconsideration is respectfully requested in view of the above amendments and following remarks.

Claim Objections

Claim 5 was objected to under 37 CFR 1.75(c) as being of improper dependent form. Applicants traverse the objection. The Examiner stated that claim 5 requires that the cells be isolated and that after step "B" of claim 12, the cells would already be isolated. Thus, the Examiner contends that claim 5 does not further limit claim 12, from which claim 5 depends. However, claim 5 recites, "wherein RNA and DNA are extracted from the isolated cells." Claim 5, recites extraction of RNA and DNA from cells, whereas claim 12 does not. Thus, claim 5 further limits claim 12 and is of proper dependent form. Removal of the objection is respectfully requested. In the alternative, if the Examiner maintains the objection, Applicants request the Examiner's assistance in making claim 5 otherwise unobjectionable.

Enablement Rejection

Before addressing the enablement rejection, it may be helpful to put the claimed invention in context. As stated in the specification (see generally page lines 12-25 of the specification), one advantage of the claimed invention is that it allows for easier identification of genes differentially expressed between primary tumors and metastatic tumors. Identification and study of such genes could prove invaluable in determining, for example, the mechanisms associated with metastatis. Prior to the claimed invention, it was not thought possible to perform meaningful gene cloning experiments on specimens of solid tumors and metastases for the purposes of identifying genes with site-specific expression. This is because it was thought impossible to separate tumor cells from normal cells without first culturing the cells and performing manipulations to get rid of the normal cells. However, the culture conditions resulted in changes in gene expression relative to *in vivo* expression. These changes in gene expression rendered gene cloning experiments for the identification of genes involved in the metastatic process meaningless. Yet without the isolation of tumor cells from surrounding normal cells, the

background gene expression of the normal cells posed similar problems. The claimed invention overcomes these problems by providing a method by which target cells can be separated from a cell population in order to identify the gene sequences from the target cells in a specific cell population environment. The successes of the claimed method were not contemplated, or even conceivable, prior to the filing of the present application.

Claims 2, 3, 5-9 and 12 have been rejected under 35 USC 112, first paragraph, for lacking an enabling specification. Applicants respectfully traverse the rejection.

The Examiner stated that "the subject specification is essentially silent as to what reaction conditions and starting materials are used in practicing the full scope of the claimed methods" and that "the situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S*.42 USPQ2d 1001." Applicants respectfully disagreee. This case does not present a situation analogous to *Genentech*. In *Genentech*, the prior art relied upon by the patentee to supplement the teachings of the specification was uncertain, perhaps contradictory, and not well established. That is not the case here. In the present situation, the specification is truly enabling in light of well-settled prior art.

The main independent claim of this application, claim 12, requires the following steps:

(A) detecting target cells from a first and a second tissue;

(B) obtaining nearly 100% specific target cells by repeatedly immunomagnetically isolating, *in vitro*, said first and second tissue target cells;

(C) determining levels of mRNA expression within said first and second tissue target cells;

(D) comparing the levels of mRNA expression in said first and second tissue target cells; and

(E) based upon the comparison in step D, identifying the genes differentially expressed between said first and second tissue target cells, wherein at least one of said first and second tissue target cells are tumor cells, in order to recognize previously unknown genes possibly involved in determining metastatic characteristics of cancer cells.

The crux of the presently claimed invention does not lie in the individual elements of the method but in novel and unobvious combination of the elements. One skilled in the art would not have contemplated or conceived of combining the elements as disclosed in the claimed method prior to this application. That is, without the present specification, one skilled in the art would not have known how to meaningfully identify genes differentially expressed between cells isolated from different tissues for the purposes of identifying genes that may be involved in the metastatic process. However, one skilled in the art had at their disposal the ability to carry out each element of the claimed method individually without reference to the present specification.

As evidence that one skilled in the art had it within their ability to (A) detect target cells from a tissue and (B) obtain nearly 100% specific target cells by repeatedly immunomagnetically isolating, *in vitro*, the target cells, the specification recites WO94/07139 and PCT/NO95/00052 on page 4, lines 25-27. As evidence that one skilled in the art had it within their ability to (C) determine levels of mRNA expression within two tissues, (D) compare the levels of mRNA expression in the two tissues, and (E) identify genes differentially expressed the two tissues, the specification recites, at page 5, line 8, Liang and Pardee, Science 257: 967-971, 1992. Many techniques such as reverse transcriptase PCR (RT PCR), RNAse protection assays, and Northern blots, differential display, and subtractive hybridization were available to the skilled artisan.

Applicants assert that the elements of the present invention could readily have been performed prior to the filing of the present application. However, as discussed above, the skilled artisan would not have conceived of combining the elements in a manner as claimed prior to the present application. Accordingly, applicants assert that upon reading the present specification one skilled in the art would have been able to use the method of the invention commensurate in scope with the claims.

As evidence of the ability of one skilled in the art to use the specification to practice the claimed invention, applicants submit two publications (Ree et al., Differential display analysis of breast carcinoma cells enriched by immunomagnetic target cell selection - gene expression profiles in bone marrow target cells, *Int. J. Cancer*, in press (2001) and Bratland et al., Expression of a novel factor, com1, is regulated by 1,25-dihydroxyvitamin D3 in breast cancer cells, *Cancer Research* **60**: 5578-5583, 2000)

showing successful use of the claimed invention. These two references serve to prove that one skilled in the art was able to apply the teachings of the present application to make and use the invention commensurate in scope with the claims.

In light of the above, applicants submit that the specification, when read in light of the knowledge available in the prior art at the time the application was filed, enables the claims. Withdrawal of the rejection is respectfully requested.

The specific claim rejections are addressed below:

1. Claim 2 was rejected as allowing the simultaneous screening of 12 or more different samples. While the scope of the invention may include the simultaneous screening of 12 or more different samples, as such a scope is well within the ability of one skilled in the art, claim 2 does not stand for such a proposition. Claim 2 simply recites some target tissues from which the first and second tissue target cells can be obtained. Any other reading is inconsistent with the claim language

2. Claims 2, 3, 7-9 and 12 were rejected as having sufficient breadth of scope to encompass conducting the assay either *in vivo* or *in situ*. Claim 12 has been amended to recite that the cells are isolated *in vitro*. One of skill in the art would understand from the specification, particularly the examples, that the claimed invention encompasses conducting the claimed invention *in vitro*.

3. Claim 7 was rejected because of the language, "any other procedure that can be used to identify genes with differential expression." This language has been deleted from claim 7 so that scope of claim 7 is limited with respect to claim 12. Claim 12 is understood to encompass a scope of identification of differential gene expression by any known method.

4. Claim 8 was rejected for requiring "one to perform sequencing reactions, identify 'interesting site-specific or site-preferred patterns'." The Examiner contends that the specification is essentially silent as to how to proceed in recognizing such sites and evaluating them. Claim 8 has been amended to recite pattern on sequencing gels revealing differential expression are sequenced and identified. Applicants assert that the one of skill in the art upon reading the specification and using well-known techniques would be able to practice the invention according to claim 8 as amended.

5. Claim 9 was rejected because the specification allegedly does not set for a repeatable procedure whereby any gene has been identified and subsequently studied. Again, applicants assert that the one of skill in the art upon reading the specification and using well-known techniques would be able to practice the invention according to claim 9.

In light of the above remarks and amendments, applicants assert that the specification enables the claims. Withdrawal of the rejection is respectfully requested.

Indefiniteness Rejections

Claims 2, 3, 5-9 and 12 were rejected under 35 USC 112, second paragraph as being indefinite. Applicants respectfully traverse the rejection to the extent that it is maintained.

Claim 6 was rejected as being indefinite for not setting forth an active step. Claim 6 has been amended to recite an active method step.

Claim 8 was rejected as allegedly being indefinite for reciting "interesting site-specific or site-preferenced patterns." Claim 8 has been amended to recite "site-specific or site-preferenced patterns revealing differential expression."

Claim 9 was rejected as allegedly being indefinite for reciting "relevant tumor sites." Claim 9 has been amended to delete the word "relevant."

Claim 12 was rejected for the presence of multiple periods. Claim 12 has been amended such that the multiple periods have been removed.

Applicants assert that in light of the amendments, the claims are definite. Withdrawal of the rejection is respectfully requested.

Obviousness Rejection

Claims 2, 3, 5-9, and 12 were rejected under 35 USC 103(a) as allegedly being obvious over Høifødt et al. in view of Smith et al (US Patent 5,776,683). Applicants respectfully traverse the rejection.

Applicants assert that the claimed invention is not obvious in light of the cited references. Further, the Smith patent is not prior art to the present application. The present application is a 371 national stage filing of a PCT application, PCT/NO97/00083,

filed March 25, 1997. The PCT application and the present application claim priority to Norwegian application 961221, filed March 26, 1996. A translation of the Norwegian application will be forwarded to the Examiner.

The Smith Patent was issued June 7, 1998, after the filing date of PCT priority application PCT/NO97/00083, which was March 25, 1997. The Smith Patent was filed on June 11, 1996, after the filing date of the Norwegian priority application. Thus, the Smith Patent is not available as prior art. Upon receipt of the translated Norwegian application, Applicants respectfully request that the Examiner withdrawal the rejection.

Høifødt et al. does not suggest the claimed invention. As stated by the Examiner, Høifødt et al. does not teach conducting differential expression analysis nor the isolation and identification of genes present in the isolated cells. Applicants assert that the claimed invention is novel in light of the Smith patent and Høifødt et al. With the Smith patent being unavailable as prior art, the Examiner must surely agree that Høifødt et al, alone, does not make the claims obvious.

Conclusion

With the above amendments and remarks, Applicants respectfully submit that the claims now pending in this patent application are in condition for allowance. Favorable consideration is respectfully requested. If any further questions arise, the Examiner is invited to contact Applicants' representative at the number listed below.

Respectfully submitted,

MERCHANT & GOULD, P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
(612) 332-5300

Dated: 11/5/01

By: _____
John J. Gresens
Reg. No. 33,112

JJG/KMC